DETAILED ACTION

Responsive to communications entered 3/28/2011. Claims 38 and 47-83 are pending. Claims 38 and 47-83 are under consideration.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/28/2011 has been entered.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 or 119 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the prior application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See Transco Prods., Inc. v. Performance Contracting, Inc., 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994) [taken from MPEP 201.01]

The instant application, 10/057,632 filed 1/25/2002 claims priority as a CON of application 09/154,354 (referred to as "the parent" filed 09/17/1998 (now PAT

6,552,031; referred to as '354) which claims benefit of provisional application 60/059,195 (referred to as "the provisional") filed 09/17/1997.

However, the following limitations are not disclosed in the earlier applications.

1. the sustained release carriers (e.g. alkylcellulose, etc.) beyond those for matrix bead formulations of claims 38,53,62 and 77.

2. sub-therapeutic doses/amounts of opioid analgesics is not found in the provisional application.

3. the oxycodone to N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]; a.k.a. T-614 throughout this office action) ratio of 0.0001-1, as set forth in new claims 82 and 83 is not found in the provisional application.

Therefore 1/25/2002 is the date for the purposes of prior art concerning claims 38,47-83.

Discussion

Page 9 last paragraph of the 3/24/2011 remarks asserts that generic support for sustained release carriers (e.g. alkylcellulose, etc.) of claims 38,53,62 and 77 may be found on pp 31-34 of the provisional and pp 34-36 of the parent application. It is noted, however said passages, in context, starting on p 30 line 9 of the provisional and p 33 line 12 of the parent each refer to *matrix-bead* formulations, yet none of the pending claims concern matrix-beads.

The 3/24/2011 remarks do not point to support in the provisional for sub-therapeutic doses/amounts of opioid analgesics nor oxycodone to T-614 in a ratio of 0.0001-1

If applicant believes this assessment is in error, applicant is to indicate as to page and line where support for each of the above limitations may be found in the earlier applications.

See also new 35 USC 112 first paragraph rejection below concerning "new matter."

Withdrawn Rejection(s)

The rejection of claims 38,47-73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement concerning "new matter," for the reasons raised in the last office action is hereby withdrawn in view of applicants amendments.

New Claim Rejection(s) – 35 USC § 112

The following is a quotation of the **first** paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38,47-83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection concerns "new matter"

Independent claims 38, 53, 63 and 77 are each drawn to methods of treating pain with T-614 and oxycodone plus various sustained release carriers (e.g. alkylcellulose, etc.)

Page 9 last paragraph of the 3/24/2011 remarks asserts that generic support for sustained release carriers (e.g. alkylcellulose, etc.) of claims 38,53,62 and 77 may be found on pp 31-34 of the provisional and pp 34-36 of the parent application. It is noted, however said passages, in context starting on p 30 line 9 of the provisional and p 33 line 12 of the parent each refer to *matrix-bead* formulations, yet none of the pending claims concern matrix-beads and read on, for instance, sustained release carrier coated tablets or capsules as well.

Applicants are reminded that it is their burden to show where the specification supports any amendments to the disclosure. See MPEP 714.02, paragraph 5, last sentence and also MPEP 2163.06 I.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP

2163.06 further notes “When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not “new matter” is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure*.

The following is a quotation of the **second** paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 55, 74-79, 83 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 55 recites the limitation "the alkylcellulose" in line 3-4. There is insufficient antecedent basis for this limitation in the claim.

The term "sub-therapeutic" in claims 75-77 is a relative term which renders the claim indefinite. The term "sub-therapeutic" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Here, it is not clear what would be deemed sub-therapeutic because, for instance a dose of narcotic (e.g oxycodone) for a child would likely insufficient for an adult; a therapeutic dose for a drug abuser, due to tolerance, would likely be higher still . The severity of pain also dictates how much narcotic is required for adequate analgesia: a therapeutic dose for individuals severely wounded on the battlefield would be considerably higher than that following minor surgery.

In accordance with MPEP 2173.02: If the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and bounds of the claim so as to understand how to avoid infringement, a rejection of the claim under 35 U.S.C. 112, second paragraph, would be appropriate. See Morton Int 'l, Inc. v. Cardinal Chem. Co., 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993).

As currently written, the metes and bounds of the claims are unascertainable. Therefore, claim 77 and all dependent claims are rejected under 35 USC 112, second paragraph.

Maintained and Updated Claim Rejection(s) – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 38, 47-52 plus 53-65 as well as 66-73 and in addition claims 74-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baker et al** (US 4569937; of record) and **Tanaka et al** (1992 Arzenimettel-Forschung 42:935-944; of record) and further in view of **Oshlack et al** US Pat. No. 5,472,712 (12/95; referred to below as '712; of record) or **Oshlack et al** US Pat. No. 6,294,195 (9/01: effectively filed 10/93 or earlier; referred to below as '195; of record) as evidenced by Beaver (1984 Combination Analgesics. The American Journal of Medicine pp 38-53; of record) or Beaver II (1992

Evaluation and Treatment of Chronic Pain Ch 29 Nonsteroidal antiinflammatory analgesics and their combinations with opioids; of record) for the reasons set forth in the previous office actions.

With regard to new claims 78-83, in accordance with MPEP 2144.05, generally differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Here, absent evidence to the contrary, the concentration ranges recited in claims 78, 79 and 80-83, which vary over 5 orders of magnitude constitute optimizations which may be determined by routine experimentation.

Response to Arguments

The 3/28/2011 remarks assert: (A) not all elements are taught; (B) there is no motivation to combine; (C) there exist secondary considerations of non-obviousness.

Applicant's arguments have been fully considered but they are not deemed persuasive for the following reasons.

(A) First, page 12 penultimate paragraph of the 3/28/2011 remarks asserts the combined references do not teach tablets or capsules.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections

are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here capsules and tablets are each provided by each Oshlack et al reference: see for instance column 1 line 39 of '195 or column 1 line 61 of '712 as well as throughout the documents. Next in the same passage, the remarks argue the claims 38, 53 and 62 exclude water as an excipient. In this vein, the examiner respectfully disagrees as follows.

Here, it is noted that independent claims 38, 53 and 62 are each drawn to a method of effectively treating pain in humans **comprising...**...orally administering… **consisting essentially of** (claim 52) or **consisting of** (claim 62). And, in accordance with MPEP 2111.02: **When the phrase "consists of" appears in a clause of the body of a claim, rather than immediately following the preamble, it limits only the element set forth in that clause; other elements are not excluded from the claim as a whole**. *Mannesmann Demag Corp. v. Engineered Metal Products Co.*, 793 F.2d 1279, 230 USPQ 45 (Fed. Cir. 1986). >See also *In re Crish*, 393 F.3d 1253, 73 USPQ2d 1364 (Fed. Cir. 2004). Here, consisting of only limits (i) T-614 and (ii) oxycodone - other elements such as water as an excipient excluded from the method claimed as a whole. In fact, claim 62 lines 3 and 13 is drawn to an admixture of excipients of which only *one* is selected from the group consisting of alkylcellulose, etc.

Furthermore, claim 53 utilizes *consisting essentially of*, which in accordance with MPEP 2105, the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and

novel characteristic(s)" of the claimed invention. *In re Herz,* 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) … For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355. Here, because there lacks of a clear indication what the basic and novel characteristic of the claimed subject matter actually concerns, the claim is therefore interpreted as comprising. Alternatively and assuming *arguendo* the basic and novel characteristic of the claimed method concerns the active ingredients T-614 plus oxycodone for pain relief, absent evidence to the contrary, the inert sustained release carrier does not provide analgesia.

In reference to 25 or 50 mg T-614, as set forth in claims 47,50,63 and 65, on p 14 first paragraph of the remarks, applicant's counsel argues the dosage for a rat at 0.96 mg/kg body mass per Tanaka et al does not apply to humans but does not provide objective evidence establishing this as a fact. And in this vein, arguments of counsel cannot take the place of evidence in the record. *In re Schulze*,346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness.") (see MPEP 2145 I.)

(B) Page 13 first full paragraph of the remarks asserts that the combined references do not teach that T-614 augments the activity of oxycodone as set forth in

claim 38,53 and 62 or a sub-therapeutic dose of claims 74-77.

In this regard, the examiner respectfully disagrees. Combination analgesia using a cyclooxygenase-2 (COX-2) inhibitor (NSAID) plus opioid (narcotic) was well known in the art well before the present invention was made: see the large numbers of examples mentioned by Baker et al in column 1 and, as mentioned in the last office action, Beaver on p 39 second paragraph, table II and, in fact, the chapter title of a textbook, that is Beaver II, showing even more NSAID plus opioid combinations, including oxycodone, which provide superior analgesia by the old idea of "cross-firing," that is enhancing efficacy by administering two drugs that produce the same effect by different mechanisms which indicates the idea of combining NSAIDs with opioids was well established in the art at the time the presently claimed invention was made.

(B) Quoting MPEP 2144.06, “In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant’s disclosure or the mere fact that the components at issue are functional … equivalents.", p 13 last paragraph of the remarks asserts there is no motivation to substitute T-614 for ibuprofen as the former has different pharmacological properties according to Tanaka et al.

This is not deemed persuasive because MPEP 2144.06 continues “…an applicant’s expressed recognition of an art-recognized or obvious equivalent may be used to refute an argument that such equivalency does not exist.); *Smith v. Hayashi*, 209 USPQ 754 (Bd. of Pat. Inter. 1980) (The mere fact that phthalocyanine and selenium function as equivalent photoconductors in the claimed environment was not

sufficient to establish that one would have been obvious over the other. However, **there was evidence** that both phthalocyanine and selenium were known photoconductors **in the art** of electrophotography. "**This**, in our view, **presents strong evidence of obviousness in substituting one for the other** in an electrophotographic environment as a photoconductor." 209 USPQ at 759.). Here, despite any differing physiological profile, as in *Smith v. Hayashi,* each of T-614 and ibuprofen are each used pharmacologically in the clinic as analgesics by inhibiting prostaglandin synthesis by in fact, inhibiting precisely the same enzyme (i.e. cyclooxygenase-2).

(C) Page 14 third paragraph asserts that more than 26 years following the filing date of the Baker reference, there is no approved product on the market comprising oxycodone and T-614.

The examiner interprets this argument as the presently claimed subject matter satisfies a long felt need. In this vein, however the following three prong test in accordance with MPEP 716.04 (I) must be satisfied:

> Establishing long-felt need requires objective evidence that an art recognized problem existed in the art for a long period of time without solution. The relevance of long-felt need and the failure of others to the issue of obviousness depends on several factors. **First, the need must have been a persistent one that was recognized by those of ordinary skill in the art.** *In re Gershon*, 372 F.2d 535, 539, 152 USPQ 602, 605 (CCPA 1967) ("Since the alleged problem in this case was first recognized by appellants, and others apparently have not yet become aware of its existence, it goes without saying that there could not possibly be any evidence of either a long felt need in the . . . art for a solution to a problem of dubious existence or failure of others skilled in the art who unsuccessfully attempted to solve a problem of which they were not aware."); *Orthopedic Equipment Co., Inc. v. All Orthopedic Appliances, Inc.*, 707 F.2d 1376, 217 USPQ 1281 (Fed. Cir. 1983) (Although the claimed invention achieved the desirable result of reducing inventories, there was no evidence of any prior unsuccessful attempts to do so.).

> **Second, the long-felt need must not have been satisfied by another before the invention by applicant**. *Newell Companies v. Kenney Mfg. Co.*, 864 F.2d 757, 768, 9 USPQ2d 1417, 1426 (Fed. Cir. 1988) (Although at one time there was a long-felt need for a "do- it-yourself" window shade material which was adjustable without the use of tools, a prior art product fulfilled the need by using a scored plastic material which could be torn. "[O]nce another supplied the key element, there was no long-felt need or, indeed, a problem to be solved".) **Third, the invention must in fact satisfy the long-felt need. In re Cavanagh, 436 F.2d 491, 168 USPQ 466 (CCPA 1971).**

Emphasis added.

Here, applicant has not presented any evidence that the long-felt need was recognized, persistent and not solved by others before the priority date of the present application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTOPHER M. GROSS whose telephone number is (571)272-4446. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571 272 0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CHRISTOPHER M GROSS
Primary Examiner
Art Unit 1636

/CHRISTOPHER M GROSS/
Primary Examiner, Art Unit 1636